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NON-ALLERGIC RHINITIS TASK FORCE

Non-Allergic Rhinitis: Position paper of the European Academy of Allergology and Clinical Immunology

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ABSTRACT

This EAACI position paper aims at providing a state-of-the-art overview on non-allergic rhinitis (NAR). A significant number of patients suffering from persistent rhinitis are defined as non-allergic non-infectious rhinitis (NANIR) patients, often denominated in short as having NAR. NAR is defined as a symptomatic inflammation of the nasal mucosa with the presence of minimal 2 nasal symptoms like nasal obstruction, rhinorrhoea, sneezing, and/or itchy nose, without clinical evidence of endonasal infection and without systemic signs of sensitization to inhalant allergens. Symptoms of NAR may have a wide range of severity, and be either continuously present and/or induced by exposure to unspecific triggers, also called nasal hyperresponsiveness (NHR). NHR represents a clinical feature of both AR and NAR patients. NAR involves different subgroups: drug-induced rhinitis, (non-allergic) occupational rhinitis, hormonal rhinitis (including pregnancy rhinitis), gustatory rhinitis, senile rhinitis and idiopathic rhinitis (IR). NAR should be distinguished from those rhinitis patients with an allergic reaction confined to the nasal mucosa, also called 'entopy' or local allergic rhinitis (LAR).

We here provide an overview of the current consensus on phenotypes of NAR, recommendations for diagnosis, a treatment algorithm and defining the unmet needs in this neglected area of research.

INTRODUCTION

The prevalence of chronic rhinitis is estimated to be as high as 30% of the total population (1). Chronic rhinitis is defined as a symptomatic inflammation of the inner lining of the nose, leading to nasal obstruction, rhinorrhea (anteriorly or posteriorly), sneezing or nasal/ocular itch. Two nasal symptoms should be present for at least 1 hour daily for a minimum of 12 weeks per year to define chronic rhinitis (1). By this definition, patients with occasional or physiological nasal symptoms are excluded, as well as those individuals with nasal inflammation beyond the nasal cavities, i.e. rhinosinusitis. Chronic rhinitis may have a spectrum of disease severity, ranging from mild to severe disease. Patients with severe chronic rhinitis unresponsive to recommended treatment are defined as having severe chronic upper airway disease (SCUAD) (2)(3). It is important to realize that rhinitis symptoms are present in those individuals with rhinosinusitis. Chronic rhinosinusitis (CRS) is reported in up to 10.9 % of the Western population (4), and defined as inflammation of the sinonasal cavities, characterized by 2 or more symptoms such as nasal obstruction, facial pain, pressure or fullness, (thick and/or discoloured) secretions, and/or decreased sense of smell (5).

Based on the knowledge of the major etiologic factor, chronic rhinitis patients are clinically dived into 4 major subgroups (Figure 1).

Infectious rhinitis is often an acute and self-limiting disease caused by a virus, usually known as common cold (5). However, infectious rhinitis may have a prolonged disease course with bacterial infection, especially in those patients with a septal perforation, nose picking and/or corpus alienum. Discolored secretions and/or crust formation are considered clinical landmarks of infectious rhinitis. It is generally accepted that infection may represent only one of the multiple underlaying factors in the pathophysiology of CRS. CRS with/without nasal polyps (CRSwNP/CRSsNP) is found in those individuals with a prolonged inflammation extending beyond the nasal cavities (5).

Allergic rhinitis is the most prevalent non-communicable disease (1), and is defined as a symptomatic inflammation of the nose induced by allergen inhalation by sensitized individuals (6). The diagnosis is based on the correspondence between the history of induction of symptoms by allergen contact and positive results of skin prick test (SPT) or allergen-specific IgE in the blood. We should recognize that a group of AR patients may have so-called ‘entopy’, i.e. an allergic reaction confined to the nasal mucosa (7). Most likely, LAR patients represent a subgroup of those formerly defined as Non-Allergic Rhinitis with Eosinophilia Syndrome (NARES).

Non-allergic, non-infectious rhinitis (NANIR) involves a heterogenous group of patients suffering of rhinitis without clinical signs of infection (discolored secretions) and without systemic signs of allergic inflammation (allergen-specific IgE in blood and/or positive SPT results). This group is often defined in short as NAR. Subgroups of NAR are: drug-induced rhinitis (8), rhinitis of the elderly (9)**,** hormonal rhinitis including pregnancy-induced rhinitis (10)**,** non-allergic occupational rhinitis (11), gustatory rhinitis (12), and idiopathic rhinitis (13). In reality, a significant portion of chronic rhinitis patients may belong to the group of so called "*mixed rhinitis*"(14). This patient population may have more than one known / unknown etiologic factors, e.g. patients with an isolated positive SPT test for pollen suffering all year long despite absence of eosinophilia in secretions. It is important to stress the importance of a precise diagnosis in this group, as a nasal endoscopy is warranted to evaluate the endoscopic signs of CRSsNP and CRSwNP that are not always obvious by anterior or posterior rhinoscopy (15)**,** as well as the anatomic factors that may contribute to the severity of the different nasal symptoms for which the patients seek medical advice (Figure 1).

PREVALENCE of NAR

Epidemiological data on NAR are limited, as we lack a uniform definition of NAR as well as an international consensus on diagnostic criteria. In addition, epidemiologic data are difficult to interpret as nasal endoscopy excluding rhinosinusitis in adults and adenoid hypertrophy in children have not been performed in the studies conducted. Despite the weakness of epidemiologic studies, it is estimated that more than 200 million people suffer from NAR worldwide (16). Within the paediatric population, Westman et al. showed an 8.1% prevalence of NAR at the age of 4 and 6.3% prevalence at the age of 8 in a Swedish birth cohort of 2024 children (17). A similar study performed in Singapore found that NAR was the diagnosis in 24.9% of 6600 children with rhinitis symptoms (mean age of 7.8 years) (18). Chiang et al. reported that NAR was more common in children under 6 years of age compared to AR while AR diagnosis increased with age and NAR decreased to 10-15% in older children (18). In Belgium, the prevalence of self-declared NAR was 9.6% in a population of 4959 subjects of 15 years or older (19). Shaaban et al. performed a longitudinal population-based study in Western Europe on the cumulative incidence of asthma in 17716 subjects during a period of 8 years. They found that the adjusted relative risk for asthma development in NAR was 2.71 (95% CI: 1.64-4.46) (20). Asthma is similarly associated with allergic and nonallergic rhinitis, but only children with AR had increased bronchial responsiveness and elevated FeNO, suggesting different endotypes of asthma associated with allergic and non-allergic rhinitis (21).

SUBGROUPS OF NAR

NAR patients may have a variety of clinical phenotypes.

At present, we recognize the following subgroups to be relevant in clinical practice:

Senile rhinitis or rhinitis in elderly

Senile rhinitis is defined as rhinitis in patients above 65 years of age, and is an underdiagnosed condition affecting up to 29.8% of the Portugese population over the age of 65 years (9). Apart from the fact that a significant portion of patients with senile rhinitis may have an allergic disease, the diagnosis of senile rhinitis most often refers to those patients with late-onset, bilateral watery nasal secretions without endonasal mucosal and/or anatomic pathology (22). A neurogenic dysregulation is considered the cause of the symptoms as ipratropium bromide, i.e. an anticholinergic drug, is effective in reducing the severity and duration of the rhinorrhea in these patients (23).

Senile rhinorrhea is a form of clear anterior rhinorrhea that affects elderly patients much more often than younger adults regardless of gender and older patients reported more drip quantitiy and more frequent drip, making rhinorrhea more bothersome and individuals more likely to seek treatment (24).

Gustatory Rhinitis

Gustatory rhinitis is characterized by watery rhinorrhea after ingestion of hot and spicy food (12). It is believed to be induced by a gustatory reflex associated with a hyperactive, non-adrenergic, non-cholinergic, or peptidergic neural system (22)**.**

Occupational Rhinitis

Occupational rhinitis is defined as an inflammation of the nasal mucosa due to exposure to a particular work environment and has to be distinguished from 'work-exacerbated' rhinitis (25). Several agents are reported to be associated with occupational rhinitis, like high and low molecular weight (HMW and LMW) allergens and irritants. HMW agents may induce a typical IgE mediated allergic inflammation, giving rise to occupational allergic disease. In contrast, the mechanisms of chronic inflammation induced by most LMW molecules remain speculative (26). The latter group of patients with non-allergic occupational rhinitis represent a subgroup of NAR. In case of prolonged

exposure to occupational agents, patients may progress to asthma (27). Therefore, recognition of occupational rhinitis is considered to be crucial in the prevention of occupational asthma. Besides occupational agents, also environmental agents like pollution and/or tobacco smoke may induce nasal symptoms via largely unknown mechanisms (11). Rhinitis can arise de novo after high-level and/or after prolonged exposure to airborne occupational or environmental irritant chemicals (28). As nonspecific nasal hyperreactivity to occupational triggers can also be found in the absence of mucosal inflammation, some authors refer to this condition as "occupational nonallergic rhinopathy (28,29).

Hormonal Rhinitis

Hormonal imbalances during menstrual cycle, puberty, pregnancy, menopause, and specific endocrine disorders such as hypothyroidism and acromegaly are often associated with NAR (30,31). Estrogens exert a vascular engorgement effect in the nose, which may lead to nasal obstruction and/or nasal hypersecretion. Beta-estradiol and progesterone increase the expression of histamine H1-receptors on human nasal epithelial and microvascular endothelial cells, and induce eosinophil migration and/or degranulation. In contrast, testosterone decreases eosinophil activation and viability (32). Although hormonal changes have a presumed etiological role especially in gestational rhinitis or pregnancy-induced rhinitis (33), the exact pathophysiology of hormonal rhinitis remains unclear and smoking appears to be the only agreed identifiable risk factor in pregnancy-induced rhinitis (30).

In new-onset allergic rhinitis and asthma after puberty it was shown, that girls with late onset of menarche were less likely to develop allergic rhinitis after puberty compared with those who have menarche at an average age (34). Late menarche (>13 years of age) was statistically significantly inversely related to allergic rhinitis development. Since the use of hormonal contraceptives was inversely associated with new-onset allergic rhinitis, the authors suggested that, in addition to endogenous hormones, hormonal contraceptives might protect young women from allergies and asthma after puberty.

Drug-induced Rhinitis

A variety of drugs may cause nasal symptoms, primarily nasal obstruction (35). Drug-induced rhinitis can be divided into two subgroups: adverse events of systemic treatment and abuse of decongestive nasal therapy, best known as rhinitis medicamentosa. The former category includes prolonged oral intake of aspirin, ibuprofen and other NSAID (36), beta blockers, sedatives, antidepressants, oral contraceptives or drugs used to treat erectile dysfunction.

Peptidergic drugs activate human mast cells through a G protein-coupled receptor, the Mas-related G protein-coupled receptor X2 (MRGPRX2) and this interaction could be responsible for some forms of drug-induced rhinitis (37).

Rhinitis medicamentosa is induced by prolonged use of potent decongestant sprays, and abrupt arrest of the use of these sprays is recommended.

Idiopathic rhinitis

Up to 50% of patients with NAR do not have a clear etiology underlying their symptoms and are so-called idiopathic rhinitis patients. The key feature of IR patients is the presence of NHR (38). Recently it was shown that the nociceptive TRPV1-substance P (SP) signaling pathway is upregulated in IR patients, most likely to be involved in the pathophysiology (13).

DIAGNOSIS OF NAR

The diagnosis of NAR is based on a detailed medical history and exclusion of clinically relevant sensitization to airborne allergens, and exclusion of clinical signs of rhinosinusitis (Figure 2).

Medical history is the key for the diagnosis of well-defined phenotypes of NAR, like senile rhinitis, gestational/hormonal rhinitis, gustatory rhinitis, occupational rhinitis and drug-induced rhinitis. Therefore, it is recommended to consider the age of the patient, the duration and frequency of symptoms, the hormonal state, the occupational/environmental exposure to a list of triggers leading to nasal symptoms, as well as the systemic and nasal medication use. All of these items may provide hints towards diagnosing the specific type of rhinitis.

Besides history, *anterior rhinoscopy* should be used to check for signs of infection, endonasal crust formation, and/or significant anatomical deformities. *Nasal endoscopy* is recommended as it allows the evaluation of the whole endonasal cavity including the ostiomeatal complex (5). The importance of nasal endosocpy in the diagnosis of prolonged courses of rhinitis cannot be underestimated, as it may reveal the presence of CRSsNP or CRSwNP.

Skin prick testing or determination of *allergen-specific IgE in the blood* is necessary for the diagnosis of AR (39). However, both SPT and determining specific IgEs in serum have their limitations. It is impossible to test all possible allergens and only the relevant are selected. On the other hand, evidence of systemic sensitization by SPT or specific IgE, does not necessarily mean that nasal symptoms are triggered by allergy. Clinical relevance of detected sensitization may be confirmed by history and/or allergen provocation test (40).

Up until now, the following diagnostic tests are *not recommended* in NAR (41):

- *Allergen provocation* testing can be performed in different ways, and is mainly performed to confirm sensitization upon specific indication in AR, OR and patients that are likely to have LAR.
- *Microbiological* analysis of the nasal content is not recommended in non-infectious rhinitis, as the presence of any virus, bacteria, or fungus does not necessarily imply infection (5).
- *Nasal cytology or biopsies* are not recommended in NAR, but may help to distinguish between an inflammatory or neurogenic etiology of symptoms (42). Detection of eosinophilic inflammation in cytology or biopsy in the absence of systemic allergy may be attributed to LAR, NARES or to intolerance to drugs (like aspirine), food or preservatives (40).
- Measurement of *total IgE or allergen-specific IgE in nasal secretions* is performed in a limited number of academic centers for the diagnosis of LAR.
- In contrast to nasal endoscopy to exclude endonasal signs of sinonasal disease, *CT scans* of the sinonasal cavities are not recommended in rhinitis patients.
- Measurement of *nasal hyperreactivity* is only performed in a limited number of academic centers beyond routine clinical practice.
- Measurement of markers of *cerebrospinal fluid* leakage (β2 transferrin or β trace) via a skull base defect are only indicated in unilateral watery rhinorrhoea

DIFFERENTIAL DIAGNOSIS OF NAR

Local Allergic Rhinitis

Local allergic rhinitis (LAR) or entopy, has been reported as a localized nasal allergic response in patients with negative SPT and absence of detectable specific IgE (sIgE) to inhalant allergens in the blood (43). In Southern Europe, almost one third of the rhinitis patients are classified into the LAR group (44). The pathophysiology is characterized by local production of sIgE, a Th2 cytokine pattern of mucosal cell infiltration (eosinophils, basophils, mast cells, CD3+ T cells, and CD4+ T cells), and a positive nasal allergen provocation test (NAPT) with release of inflammatory mediators (tryptase and eosinophil cationic protein) (40). There is evidence of an allergen-specific basophil activation in peripheral blood, suggesting that this cell can be the first or only target for sIgE after its nasal production (45). A history of "AR type" symptoms elicited by natural exposure to aeroallergens is usually present. The diagnosis of LAR can be confirmed by the detection of nasal sIgE, a positive NAPT response, or both (46). The NAPT is a key tool for the diagnosis although it is time consuming. NAPT with multiple aeroallergens (NAPT-M) in one session has proved to be specific, sensitive, reproducible and less time-consuming (75% reduction in the number of visits for diagnosis of NAR, and a 55% for LAR) (46). Basophil activation test in peripheral blood (45) is very specific, less time-consuming and supports the diagnosis of LAR.

Medical management of LAR is similar to AR, with good response to nasal corticosteroids. Due to its' cost and complexity, NAPT or detection of specific IgE in nasal secretions are not recommended in clinical practice. As a consequence, a percentage of patients with LAR are still be classified into the NAR group in every day clinic.

Conditions mimicking NAR

Amongst the conditions mimicking NAR, we should acknowledge the rare condition of a post-traumatic or spontaneous skull base defect with leakage of cerebrospinal fluid (CSF), giving rise to (unilateral) watery discharge from the nose. CSF leakage should be considered in those patients with a relevant history and rhinorrhoea not responding to nasal corticosteroids, ipratropium bromide or capsaicin nasal treatment (47).

CRSsNP and CRSwNP should not be overlooked in patients with NAR, as symptomatology between NAR and CRS patients may overlap in part. Nasal endoscopy is the preferred means of diagnosis of CRS, and CT scans should be reserved for those patients with suspicion of CRS and without nasal endoscopy available (3).

DIAGNOSTIC CHALLENGE OF NASAL HYPERREACTIVITY

The induction of one or more nasal symptoms upon encounter of unspecific environmental stimuli, such as smoke, temperature/humidity changes, strong odors and other irritants, is called nasal hyperreactivity (NHR). NHR is a key clinical feature of both AR and NAR (48), and is mainly defined by the history of the patient. Several diagnostic tests have been developed to quantify NHR, like nasal exposure to hyperosmolar solution (49), nasal histamine (50) or cold dry air (CDA) (38)(51). CDA represents a physiological, safe and tolerable stimulus for the nasal mucosa, and has been proven to be a good diagnostic tool for NHR (52). Braat et al. demonstrated that CDA provocations were superior to nasal histamine provocations in discriminating IR patients from healthy controls, as histamine provocation did not allow the discrimination between IR patients and controls (51). Sensitivity for CDA was 87% compared with 100% for histamine, but specificity was 71% for CDA and 0% for histamine (51). The protocol used in the latter study is time-consuming, therefore a short protocol of CDA exposure with high sensitivity and specificity for the demonstration of NHR in AR and IR was recently validated (38). At present, more studies on CDA nasal provocation studies are warranted in order to confirm the validity of this technique and to study NHR in different patient populations and controls. There is now growing consensus about the usefulness of such a technique in daily practice as NHR often remains undiagnosed and cannot be taken into account in trials evaluating the effects of medical treatment for rhinitis.

ENDOTYPES OF NAR

As NAR involves a variety of conditions, the pathophysiology may vary but can roughly be divided into a classic inflammatory pathway, neurogenic pathway and other (largely unknown) pathways.

The inflammatory pathway is found in a subgroup of NAR patients. A Th2 cytokine inflammatory pattern is found in AR patients, as well as in those with occupational allergic rhinitis induced by High Molecular Weight (HMW) allergens. These patients do generally not cause a therapeutic challenge as they respond well to nasal corticosteroid treatment, as is the case in LAR

patients. However, several patients with NAR do not have an influx of inflammatory cells in the nasal mucosa, and are believed to have a neurogenic mechanism involved, including rhinitis of the elderly, gustatory rhinitis, some forms of occupational rhinitis, some forms of drug-induced rhinitis and IR (13)(26)(53).

The neural regulation of the upper airways is complex and consists of a number of interacting nervous systems (42). Sensory, parasympathetic and sympathetic nerves regulate epithelial, vascular and glandular processes in the nasal mucosa (53). The anatomically defined sensory, parasympathetic and sympathetic neural systems contain heterogeneous populations of nerve fibers often containing unique combinations of neuropeptides (54). Some phenotypes seem to be based on a relatively simple regulatory disorder, like rhinitis of the elderly that mostly seems to be a dysregulation of the parasympathetic / sympathetic neural dysbalance and can be treated with the anticholinergic drug ipratropium bromide (55) or rhinitis medicamentosa, resulting in dysregulation of adrenergic receptors in nasal mucosa and in a relative increase of the parasympathetic drive, leading to significant rhinorrhea and nasal obstruction (35).

Solitary chemosensory cells of the nasal cavity are specialized epithelial chemosensors that respond to irritants through the canonical taste transduction cascade stimulating peptidergic trigeminal nociceptive (or pain) nerve fibers (56). Activation of these nasal cells can trigger similar local inflammatory responses (mast cell degranulation and plasma leakage) like direct chemical excitation of trigeminal pain fibers using capsaicin and this only by cholinergic neurotransmission and neural activity and not by release of local inflammatory mediators (56).

IR is thought to be a disorder of the Non-adrenergic Non-cholinergic (NANC) or peptidergic neural system (42)(57). Perivascular and intra-epithelial non-adrenergic non-cholinergic (NANC), sensory nerve fibres contain neuropeptides (including VIP, substance P (SP), calcitonin gene related peptide (CGRP). These neuropeptides are locally released from peptidergic neurons (anti-dromic release), mainly unmyelinated sensory C-fibres, in the nasal mucosa after activation by unspecific stimuli, and can be responsible for the symptoms of IR (57). Stimulation can be induced by inflammatory mediators, like histamine and bradykinin but also by a number of inhaled irritants like nicotine, chlorine, formaldehyde and capsaicin, mostly via the TRPA1 and TRPV1 receptor. Recently was shown that the nociceptive TRPV1- SP signaling pathway is upregulated in IR patients (13).

THERAPEUTIC ALGORITHM for NAR

NAR patients constitute a group of patients with different phenotypes, with variable severity, underlying etiology and type of inflammation. The phenotypes warrant different treatment strategies depending on the etiology. However, most of the studies on treatment for NAR have been performed in unselected NAR patients. It makes sense to link the therapeutic strategy to the known or suspected underlaying etiology, being inflammation, neurogenic dysfunction, environmental exposure and/or medication use (Figure 3).

The inflammatory group (occupational rhinitis and drug-induced rhinitis) may benefit from anti-inflammatory treatment like nasal/oral corticosteroids and/or nasal/oral antihistamines. However most RCTs evaluating local corticosteroids in NAR patients showed a lack of efficacy. Only 2 studies (58)(59) comprising 101 patients showed a positive outcome, whereas all other studies comprising more than 1000 patients did not show a major benefit of nasal corticosteroid treatment (60)(61)(62). Interestingly 2 double-blind, placebo-controlled trials have been published showing a therapeutic effect for azelastine nasal spray in NAR patients (63)(64). The precise mode of action (antihistaminic, antiinflammatory, or otherwise) remains to be elucidated.

Treatment of the drug-induced phenotypes of NAR primarily will consist of avoidance of the drug. Aspirin intolerant individuals may benefit from aspirin desensitisation (65)(66)(67,68).

Irritant avoidance and smoking stop should be advised to all rhinitis patients, and more specifically in those with occupational and IR (69).

The treatment of non-inflammatory phenotypes of NAR is diverse depending on the presumed pathophysiology. Ipratropium bromide is an anticholinergic drug and the first treatment option in rhinitis in the elderly (23). Several studies have been published showing that repeated administration of capsaicin in a double-blind, placebo-controlled trial led to a significant long-term reduction of symptoms in patients with IR (70)(71)(72). Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is the active component of plants of the genus Capsicum like chili peppers. Capsaicin is unique among naturally occurring irritant compounds because the initial neuronal excitation evoked by it is followed by a long-lasting refractory period, during which the previously excited neurons are no longer responsive to a broad range of stimuli (73). Recent data provided more insight in the working mechanisms of this beneficial effect of capsaicin (13).

Capsaicin reduces the density of the innervation of the nasal mucosa and the TRPV1-SP signaling pathway, without affecting the integrity and function of nasal epithelial cells or mast cells, and in this way improved the symptoms in 80% of well-selected IR patients (13), but Capsaicin has not been shown to be effective in allergic rhinitis nor in other forms of non-allergic rhinitis like the inflammatory endotypes or other neurogenic endotypes like rhinitis of the elderly or smoking induced rhinitis (73).

Intranasal administration of a selective intranasal TRPV1 antagonist in patients with IR induced a marked reduction in total symptom scores triggered by nasal capsaicin challenge (74). When medical treatment fails or in case of severe nasal obstruction with hypertrophy of the inferior turbinates, a surgical intervention like turbinate reduction (75) may be considered. Severe IR patients may respond well to a vidian neurectomy (76), but this intervention is rarely performed.

In summary treatment of NAR should be adapted as much as possible to the underlaying etiology.

UNMETS NEED IN NAR

NAR represents a heterogenous group of mucosal pathology of variable severity and with a heterogenous underlaying etiology. In spite of the fact that NAR is not life-threatening, patients consulting their doctor mostly suffer from a severe condition. Despite all efforts in listing the unmet needs by the international expert community (16), the following unmet needs still need to be addressed during the next decade:

- prevalence studies on NAR, including phenotyping and endotyping, with evaluation of the associated conditions and SCUAD amongst the NAR population
- exploration of the pathophysiology of NHR, with improving the therapeutic approach of NHR
- international consensus on the optimal and most cost-effective diagnostic approach of NAR patients
- properly conducted trials on the efficacy of different medical treatment options in NAR patients with clear diagnostic inclusion and exclusion criteria
- insight into the mechanisms of nasal hyperreactivity in different subgroups of NAR
- endotype-driven treatment for NAR
- positioning the role of turbinate reduction in NAR, with emphasis on the precise indication and expected outcomes after surgery

CONCLUSION

NAR represents a nasal condition with high prevalence, variable etiology and severity, and a wide array of different treatment options. However, only limited studies are available exploring the real-life epidemiology, pathophysiology and therapeutic outcomes of the different subgroups of NAR. The availability of novel tools for measuring NHR as well as the increased insight into the pathophysiology of different types of NAR, will lead to a better treatment strategy of this condition.

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FIGURE LEGENDS

Figure 1. Phenotypes of Chronic Rhinitis.

Figure 2. Diagnosis of Chronic Rhinitis.

Figure 3. Therapeutic strategy of Non-Allergic Rhinitis.